iii) **CNS toxicity** (e.g., agitation, confusion): reduce dose (Cp)
iv) **GI** (nausea, vomiting, diarrhea): reduce dose; try extended-release product, split doses
v) **Hypothyroidism**: discontinue Li or give levothyroxine
vi) **Polydipsia or polyuria**: Reduce dose, manage intake, and try amiloride or HCTZ, but HCTZ will ↑ Li Cp; single bedtime dosing helps
vii) **Interstitial fibrosis, glomerulosclerosis**: Keep dose at lowest effective concentration; avoid dehydration
viii) **Teratogenicity**: Avoid during first trimester, if possible

2) **Anticonvulsants for Bipolar Disorder**

✓ **Valproate**: As effective as lithium in acute and prophylactic management. It appears to be good for rapid cyclers but may not be as effective during depressive episodes. It is also beneficial for patients with dysphoric mania, mixed episodes, or a history of substance use disorder. Toxicity can happen by co-administering with highly protein-binding drugs (e.g. aspirin). Side effects include: sedation, GI distress, benign hepatic transaminase elevation, weight gain, hair loss, and rarely acute pancreatitis (in children), & polycystic ovary disease. Use in pregnancy has been associated in neural tube defects in the fetus. Dosing: 1) in mild forms, start with 250 mg po tid and increase the dosage as needed till the patient stabilizes. 2) in acute mania: load the patient up to 20mg/kg/day.

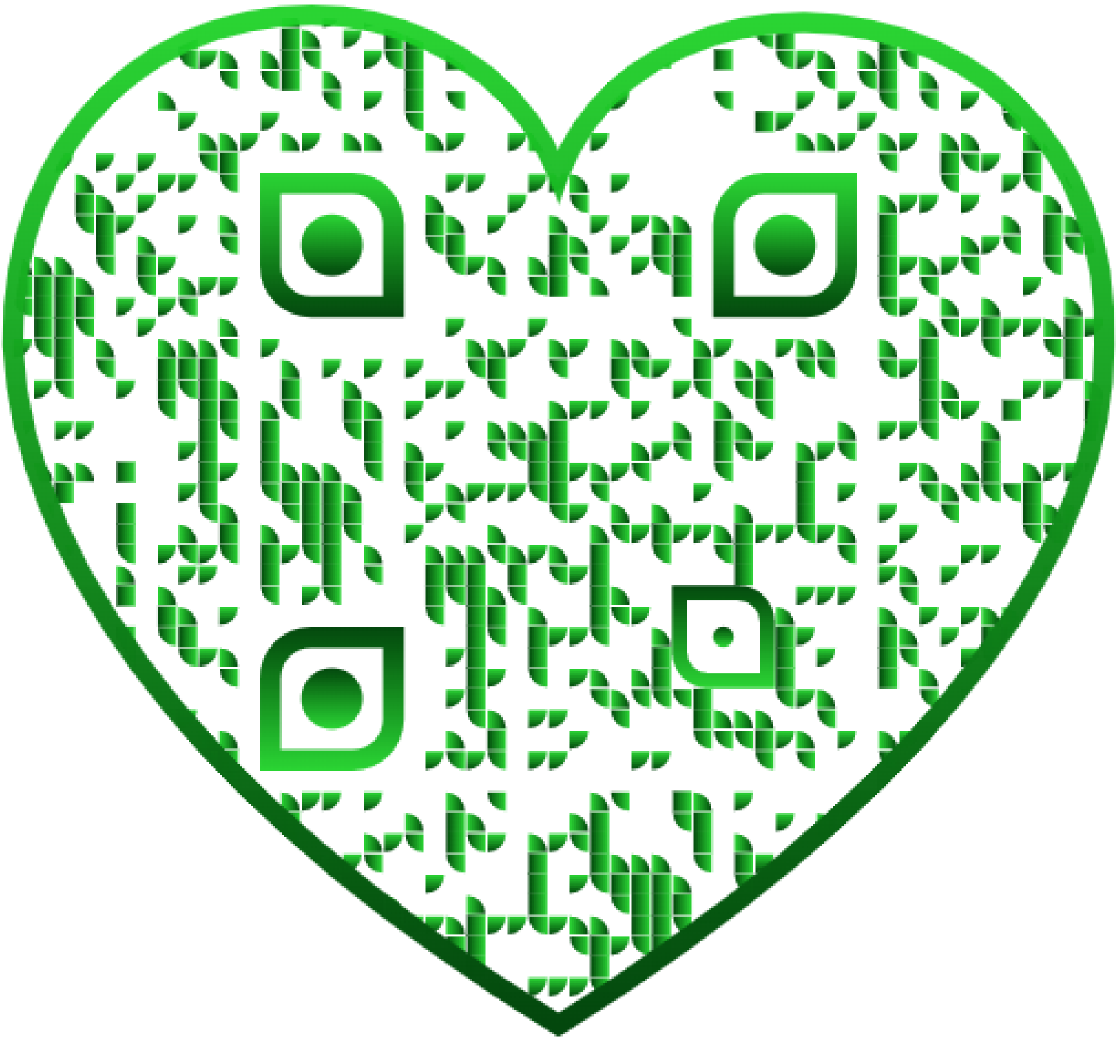
✓ **Carbamazepine**: Effective for acute mania and maintenance therapy, particularly in patients with a history of head injury. Carbamazepine can abe added to lithium for patients who have not responded to monotherapy.

✓ **Lamotrigine**: It appears particularly effective for the prevention of future depressive episodes of bipolar disorder. It is less effective than other mood stabilizers for the prevention of the manic phase. A Stevens-Johnson type rash occurs in about 0.3% of adults and 1% of children. The dose titration must be halved if lamotrigine is given with valproate and doubled if given with carbamazepine because of increased lamotrigine metabolism. Lamotrigine has been associated with aseptic meningitis in adult and pediatric patients.

✓ **Other anticonvulsants**, including levetiracetam, oxcarbazepine, and topiramate, are used for bipolar disorder, but data regarding their efficacy are scarce

3) **Antipsychotics for Bipolar Disorder**

✓ Antipsychotics, particularly SGAs, have mood-stabilizing properties. They can be used alone or with anticonvulsant mood stabilizers to treat bipolar symptoms. Metabolic adverse effects associated with



antipsychotic use should be considered when medications are administered long term

- ✓ Acute treatment: Antipsychotics treat acute symptoms of mania, including psychosis, aggression, and irritation. They are often combined with a traditional mood stabilizer for severe symptoms. All SGAs are indicated for use in acute mania or mixed episodes except for brexpiprazole, clozapine, and iloperidone.
- ✓ Bipolar depression: Both quetiapine and lurasidone are approved for treatment of bipolar depression. Olanzapine is also approved for treatment of bipolar depression when combined with fluoxetine. Data for aripiprazole suggest it is ineffective for the treatment of bipolar depression.
- ✓ Maintenance treatment: The long-acting injectable antipsychotic formulations of risperidone and aripiprazole have been approved for use in bipolar maintenance as monotherapy.

4) **Benzodiazepines for Bipolar Disorder:**

- ✓ These agents are acutely helpful for agitation but are not as helpful for the core symptoms, nor do they prevent relapses.

7.4. Attention Deficit Hyperactivity Disorder (ADHD)

✍ Introduction

- Once considered primarily a childhood disorder, ADHD is now known to persist into adolescence for 75% and into adulthood for approximately 50% of individuals. Co-occurring anxiety, mood disorders, learning disabilities, medical conditions, and substance use disorders must be considered in assessment and treatment. The psychiatric assessment of a child requires obtaining information from the child, parents, caregivers, and teachers

✍ Epidemiology

- ADHD is the most well-known and researched neurodevelopmental disorder of childhood. It occurs in approximately 5% to 10% of children and approximately 2.5% to 5% of adults. ADHD is more prevalent in males than females with a ratio of 2:1 in children and 1.6:1 in adults

✍ Diagnostic Criteria for ADHD

- **Inattention**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities. Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required. **a)** Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate); **b)** Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading) **c)** Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction); **d)** Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked); **e)** Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines; **f)** Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers); **g)** Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones); **h)** Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts); **i)** Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

- Hyperactivity and impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities. Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required. **a)** Often fidgets with or taps hands or feet or squirms in seat; **b)** Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place); **c)** Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.) **d)** Often unable to play or engage in leisure activities quietly; **e)** Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with); f) Often talks excessively; **g)** Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation); **h)** Often has difficulty waiting his or her turn (e.g., while waiting in line); **i)** Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

> **Key Concepts** *In many ADHD patients, hyperactive and impulsive symptomology tend to decrease with age; however, inattention is persistent throughout the lifespan.*

✍ ADHD: Subtypes

1) ADHD predominantly inattentive type: criteria met for inattention but not for impulsivity/hyperactivity
2) ADHD predominantly hyperactive-impulsive type: criteria met for impulsivity/hyperactivity but not for inattention
3) ADHD combined type: riteria are met for both inattention and impulsivity/hyperactivity

✍ Pathophysiology of ADHD

- Specific etiology unknown
- Neuroimaging has revealed anomalies (both volume and metabolic activity) in the frontal cortex and basal ganglia
- Biochemical basis is not fully known
- Neurochemistry of ADHD: Both dopaminergic (DA) and noradrenergic (NE) systems are strongly implicated in the pathophysiology of ADHD.

✍ Potential Areas of Impairment

a) ADHD may result in performance limitations
  - ✓ Significantly more academic difficulty in school (25% repeat a grade)
  - ✓ Lower levels of occupational advancement

b) ADHD affects socialization
  - ✓ Children are stigmatized by their behavior
    - ➯ Disruptivebehavior: troublemakers, excessive talking, unfocused, not responsive to others, bad sportsmanship, cannot sit still, impulsive aggression
    - ➯ Immaturity and impulsiveness: center of attention, blurting out answers, breaks the rules, peer rejection
  - ✓ Adolescents continue to demonstrate social problems
    - ➯ Poor participation in group activities
    - ➯ Few friends
    - ➯ Vulnerable to antisocial groups, drug abuse

✍ Treatment

- Stimulants
  - ✓ Stimulants are broadly divided into two main chemical classes, ***methylphenidate*** (includes dexmethylphenidate) and ***amphetamines*** (includes dextroamphetamine and mixed amphetamine salts).
  - ✓ Methylphenidate and amphetamines block presynaptic dopamine and norepinephrine reuptake; amphetamines also increase dopamine release. Both drugs inhibit monoamine oxidase (MAO), amphetamines more potently than methylphenidate. Because different stimulants work through slightly different mechanisms, the lack of response to one chemical class of stimulant (eg, methylphenidate or dexmethylphenidate) does not preclude response to another class (eg, mixed amphetamine salts, dextroamphetamine, or lisdexamfetamine)
  - ✓ New Stimulant Formulations

1) **Focalin**™: a refined form of Ritalin®, isolating only the effective isomer
2) **Ritalin**® LA: **QD** formulation of Ritalin® (**Methylphenidate**) that mimics BID dosing and duration and designed to last the school day (8-9 hrs)
3) **Adderall** XR™: extended-release formulation of mixed amphetamines (**Amphetamine-dextroamphetamine**) that mimics BID (12 hrs)
4) **Metadate**® CD: **methylphenidate** formulation designed to mimic BID duration (8-9 hours)
5) **Concerta**®: **methylphenidate** formulated to mimic TID duration (12 hr)

- Potential side effects of stimulants: appetite loss, abdominal pain, insomnia, nervousness, mild increase in pulse and blood pressure, psychiatric effects (irritability, dysphoria, and rebound)

7.5. Substance Use Disorders

1. Alcohol

✍ Defining the "Standard Drink"

- ✓ A standard drink = 14 g ethanol. This means 12 oz of regular beer or cooler (5% alcohol), 5 oz of table wine (12% alcohol), 1.5 oz of hard liquor (40% alcohol, 80 proof). The average person metabolizes about 1 standard drink per hour. It is metabolized by 2 enzymes: alcohol dehydrogenase (ADH) & aldehyde dehydrogenase. ADH catalyzes the conversion of alcohol into acetaldehyde. Women have a lower ADH content than men which may account for women's tendency to become more intoxicated.

✍ The World Health Organization estimates that some 2.348 billion people (43% of the population) were current drinkers in 2016.[1] In Ethiopia, current and lifetime prevalence of alcohol consumption was reported to be 23.86% and 44.16%, respectively.[1]

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[1] World Health Organization. **Global status report on alcohol and health 2018. Geneva**: World Health Organization; 2018.

✍ Alcohol Abuse

- Maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested within a 12-month period by at least 1 of the following:
  - ✓ Failure to fulfill role obligations at work, school, or home
  - ✓ Recurrent use in hazardous situations
  - ✓ Legal problems related to alcohol
  - ✓ Continued use despite alcohol-related social or interpersonal problems

✍ Alcohol Dependence

- Maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested within a 12-month period by at least 3 of the following:
  - ✓ Tolerance
  - ✓ Withdrawal
  - ✓ Loss of control over amount of alcohol consumed
  - ✓ Preoccupation with controlling drinking
  - ✓ Preoccupation with drinking activities
  - ✓ Impairment of social, occupational, or recreational activities
  - ✓ Use is continued despite persistent problems related to drinking

✍ Acute withdrawal

- Characteristic symptoms occur after alcohol discontinuation.

Table 7.4 Stages of acute alcohol withdrawal[2]

Stage	Onset	Symptoms
1	6–12 hr	Mild tremors, irritability, mild agitation, restlessness, tachycardia, nausea, sweating
2	12 – 24 hr	Marked tremors, hyperactivity, hyperalertness, increased startle response, pronounced tachycardia, insomnia, nightmares, illusions, hallucinations, alcohol cravings
3	12 – 48 hr	More severe symptoms than during stage 2; seizures may occur
4	3 – 5 days	Delirium tremens: Confusion, agitation, tremor, insomnia, tachycardia, sweating, hyperpyrexia

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[1] Ayano G, Solomon M, Hibdiye G, Duko B: **The epidemiology of tobacco use in Ethiopia: a systematic review and meta-analysis.** *Journal of Public Health* 2020.

[2] Bondi DS, Bridgeman MM, Burke JM, et al. **Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course,** 2021 ed. Lenexa, KS: American College of Clinical Pharmacy, 2021

- **Treatment of acute alcohol withdrawal**
  - ✓ Because of cross-tolerance, benzodiazepines can be used therapeutically to prevent and/or treat withdrawal symptoms

Table 7.5 Benzodiazepines for acute alcohol withdrawal

Drug	Fixed-dose regimen	Comments
Lorazepam	2 mg every 6 hr x 4; then 1 mg every 6 hr x 8	**Preferred** medication, particularly for liver disease; no active metabolite
Diazepam	10 mg every 5 hr x 4; then 5 mg every 6 hr x 8	Decrease dose for liver disease
Chlorodiazepoxide	50 mg every 6 hr x 4; then 25 mg every 6 hr x 8	Long acting, decrease dose for liver disease

- **Nutritional considerations**
  - ✓ **Thiamine**: This should be given to all patients to prevent Wernicke-Korsakoff syndrome – 100 mg intramuscularly on admission and then orally for 3 days
  - ✓ **Electrolytes**: Assess by serum chemistry and add to intravenous solutions as indicated (e.g., potassium).
  - ✓ **Vitamins**: These patients are usually undernourished; multivitamin may be indicated (folate and vitamin B12 should be monitored).
  - ✓ **Fluid therapy**: The patient may initially be overhydrated, but usually, fluid deficit will follow; replace fluids, usually with intravenous 5% dextrose solution with half-normal saline plus other electrolytes (e.g., potassium, phosphate)
  - ✓ **Seizures**: Benzodiazepines will usually prevent seizures
- **Other agents**
  - ✓ β-Blockers: These agents help with tremor, HR, and BP.
  - ✓ α-Agonists (e.g., clonidine): may help with some of the withdrawal symptoms

✍ **Chronic therapy**

- **Disulfiram**: This drug blocks acetaldehyde dehydrogenase, and if alcohol is used with it, the person will develop symptoms that include nausea/vomiting, flushing, and headache, among others
- **Naltrexone**: This drug can also be used chronically and has been shown to reduce cravings
- **Acamprosate**: This drug is a structural analog of GABA. It, too, reduces cravings

2. Opioid Dependence

- Globally 40·5 million people were dependent on opioids and 109,500 people died from opioid overdose in 2017.[1]
- Opioid withdrawal is not life threatening in the absence of concomitant medical conditions. Early symptoms may resemble flu and include agitation, anxiety, muscle aches, yawning, sweating, rhinorrhea, and lacrimation. Later symptoms include abdominal cramping, diarrhea, piloerection, dilated pupils, nausea, and vomiting.
- Pharmacologic therapies for opioid addiction include maintenance therapy with methadone, an opioid agonist; antagonist therapy with naltrexone; detoxification with medications given in rapid taper (e.g., methadone, buprenorphine, or clonidine) to prepare the patient for antagonist or counseling therapy; and partial agonist therapy with buprenorphine or buprenorphine/naloxone.

3. Tobacco Dependence

- Gobally, 942 million men and 175 million women ages 15 or older were smokers in 2015.2 The prevalence of current tobacco smoking was 6.67%, and lifetime smoking was 11.98% according to a systematic review and meta-analysis in Ethiopia.3
- Tobacco use is the main cause of preventable morbidity and mortality. Tobacco use increases the risk of cardiovascular disease (including stroke), chronic obstructive pulmonary disease, and cancer (both lung and non-lung). A usual pack contains 20 cigarettes
- Nicotine replacement therapy: All forms are equally efficacious. Patients should be advised to stop smoking completely before initiating. Nicotine replacement therapy is available in the following forms:

  a) Patch: For patients who smoke more than 10 cigarettes/day, start with 21 mg/day for 2 weeks, then 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks. Those who smoke 10 cigarettes/day or less, start with 14 mg/day for 6 weeks, then 7 mg/day for 2 weeks. Patches may be used for longer periods, if needed, to improve success. It is recommended to change the patch when awakening every day. Rotate sites.

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[1] Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, Bruneau J, Altice FL, Henderson G, Rahimi-Movaghar A *et al*: **Global patterns of opioid use and dependence: harms to populations, interventions, and future action.** *Lancet* 2019, **394**(10208):1560-1579

[2] Drope J, Schluger N, Cahn Z, Drope J, Hamill S, Islami F, Liber A, Nargis N, Stoklosa M. 2018. **The Tobacco Atlas**. Atlanta: American Cancer Society and Vital Strategies.

[3] Ayano G, Solomon M, Hibdiye G, Duko B: **The epidemiology of tobacco use in Ethiopia: a systematic review and meta-analysis.** *Journal of Public Health* 2020.

b) Gum: The gum should be chewed until a "peppery" or flavored taste develops; then the gum should be "parked" between the cheek and gum to facilitate buccal absorption. The gum should be chewed and parked for 30 minutes or until the flavor is gone. The maximum number of pieces of gum is 24 pieces in 24 hours. Patients who smoke 25 cigarettes/day or more should use the 4-mg dose. Those who smoke fewer than 25 cigarettes should use the 2-mg dose. One piece of gum should be used every 1–2 hours for the first 6 weeks of therapy, followed by 1 piece every 2–4 hours for weeks 7–9, then 1 piece every 4–6 hours for weeks 10–12. Acidic beverages (e.g., coffee, juices, and soft drinks) interfere with buccal absorption and should be avoided at least 15 minutes before using the gum. Adverse effects include soreness, dyspepsia, hiccups, and jaw ache.

c) Lozenge: Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength. Otherwise, the 2-mg dose is used. The lozenge should be dissolved in the mouth rather than chewed or swallowed. The frequency of use and tapering are the same as for the gum. Adverse effects are also similar. At least 9 lozenges should be used at the beginning to increase chances of quitting. Only 1 lozenge should be used at one time. No more than 5 lozenges within 6 hours, maximum 20 lozenges/24 hours

? REVIEW QUESTIONS

1. Alcohol withdrawal detoxification is by using:
   A. Benzodiazepines B. SSRIs
   C. Atypical antipsychotics D. Amphetamine
2. 19 years of girl has symptoms with the following features; which one is **incorrectly** matched?
   A. Aggressive symptoms: Anhedonia, avolition, alogia
   B. Grandiose ideation: she believes that she is a top model
   C. Delusion: Worms and snakes in her stomach, feet were cut off, being raped (all these are not actual)
   D. Hallucination: Her late grandfather is telling her to burn their home
3. One of the following second-generation antipsychotics has a different mechanism of action than the others:
   A. Clozapine B. Resperidone C. Aripriprazole D. Ziprazidone
4. All of the following are effects of tricyclic antidepressants; except:
   A. Sedation B. Hypertensive crisis
   C. Constipation D. Dry mouth
5. Currently, the antidepressants of choice are:
   A. MAOIs B. TCAs C. SSRIs D. NaSSA

6. From the five symptom dimensions in schizophrenia, which symptom overlaps with positive symptoms?
A. Cognitive B. Negative C. Aggressive D. Depressive
7. Of the first-generation antipsychotics, which one is least potent of the rest?
A. Fluphenazine B. Trifluoperazine C. Haloperidol D. Chlorpromazine
8. At normal CNS state which of the following statements is correct on the balance of NE, 5HT, DA and Ach?
A. DA controls Ach release B. 5HT controls DA release
C. NE controls 5HT release D. All of the above
9. The atypical antipsychotic agent known by its agranulocytosis SE is:
A. Aripripradole B. Clozapine C. Olanzapine D. Resperidone
10. The first line options in the management of bipolar disorder are:
A. Lithium and valproic acid
B. Lithium and Antiepileptic agents
C. Valproic acid and Atypical antipsychotics
D. Valproic acid and Antiepileptic agents
11. The two main symptoms of depression are:
A. Depressed mood and loss of interest
B. Decreased energy and feeling guilty
C. Loss of appetite and sleep disturbance
D. Suicidal ideation and loss of confidence
12. A low-grade but very chronic form of depression is
A. Hypomania B. Dysthymia
C. Double depression D. Mixed episode
13. SSRIs could not be used in the management of
A. Depression B. Sleep disorder C. Anxiety D. None
14. True about lithium:
A. It is safe for CKD patients B. TDM is not indicated for lithium
C. It can treat pregnant woman D. It can be used in CLD patients
15. In the time course of ADHD,
A. Inattention diminishes with aging
B. Hyperactivity increases with aging
C. Impulsivity diminishes with aging
D. All the symptoms persist with aging
16. Which of the following statements most accurately describes the clinical presentation of adult ADHD?
A. Hyperactivity and impulsivity are the most prominent symptoms.
B. Adults frequently report racing thoughts, mood swings, and insomnia.
C. Disorganization increases in frequency and severity during adulthood.
D. Distractibility and difficulty with sustained mental effort are most common.

17. A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?
    A. Diazepam B. Pentobarbital. C. Phenytoin D. Buspirone.
18. A 36-year-old man presents with symptoms of compulsive behavior. If anything is out of order, he feels that "work will not be accomplished effectively or efficiently." He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which of the following drugs would be most helpful to this patient?
    A. Imipramine. B. Fluoxetine C. Amitriptyline. D. Lithium.
19. Which one of the following neuroleptics has been shown to be a partial agonist at the D2 receptor?
    A. Aripiprazole B. Clozapine C. Haloperidol D. Risperidone
20. A 28-year-old woman with schizoid affective disorder and difficulty sleeping would be most benefited by which of the following drugs?
    A. Aripiprazole. B. CPZ C. Haloperidol. D. Risperidone
21. Which of these statements is true when giving advice on sleep hygiene?
    A. Drinking coffee and tea is OK before bedtime
    B. Try to vary the time when you go to bed
    C. Try not to nap through the day
    D. Take light exercise before going to bed
22. Which of the following laboratory test should be monitored frequently to assess for a potential life-threatening adverse reaction to clozapine?
    A. Renal function test B. Complete blood count
    C. Liver function test D. Thyroid function test
23. The preferred treatment option for a 20-year-old patient with bipolar disorder who has severe liver disease is:
    A. Valproic acid B. Lithium C. Carbamazepine D. Oxcarbazepine
24. All of the following are symptoms of acute mania except:
    A. Grandiosity B. Racing thoughts
    C. Decreased appetite D. Pressured speech
25. Antipsychotics could be used in a patient displaying which of the following symptoms?
    A. Mania with psychotic features B. Mania without psychotic features
    C. Depression with psychotic features A. All of the above
26. M.P. is a 33-year-old woman who comes to the psychiatric clinicTikur Anbessa Specialized Hospital for a follow-up of her first episode of major depression. She has taken citalopram 20 mg orally daily for 8 weeks with partial symptom relief. She takes no other medications, and her laboratory values are all normal. M.P. states that she still feels sad and is uninterested

in many activities but that she is sleeping better and has returned to work. She is tolerating the medication well. Which intervention is most appropriate for M.P.?

A. Continue citalopram 20 mg/day. B. Increase citalopram.
C. Add amitriptyline at bedtime. D. Change to mirtazapine at bedtime.

27. R.R. is a 23-year-old woman who arrives at the psychiatric clinic at Zewuditu Memorial Hospital for a follow-up after her first episode of schizophrenia. She has taken risperidone 3 mg orally twice daily for 6 weeks with an overall decrease in hallucinations, but ongoing auditory hallucinations are affecting her ability to concentrate on tasks. She has stiffness in he joints, and psychomotor retardation is present. Which treatment is most appropriate?
A. Increase risperidone.
B. Increase risperidone and add benztropine.
C. Decrease risperidone and add olanzapine.
D. Change to olanzapine.

28. K.K. is a 35-year-old man with a diagnosis of schizophrenia who has taken several antipsychotics during his 15 years of illness. He now takes olanzapine 20 mg orally at bedtime. To ensure the safety and tolerability of olanzapine, which monitoring value or group of monitoring values is best to obtain routinely?
A. Thyroid-stimulating hormone.
B. Serum creatinine and blood urea nitrogen.
C. Fasting blood glucose and total lipid profile.
D. Prolactin concentration.

Questions 29 –31 pertain to the following case.

T.R. is a 59-year-old man seen in the ambulatory care clinic for a follow-up of hypertension, heart failure, and atrial fibrillation. Five years ago, he had a myocardial infarction. His blood pressure is stable and in goal range with lisinopril, metoprolol, and furosemide. He has maintained a normal sinus rhythm with amiodarone. He has a long history of bipolar I disorder, for which he takes lithium and divalproex. His most recent mood episode was depression 6 months ago. Today in the clinic, he is hyperactive and hyperverbal; he reports not sleeping for the past few nights and has racing thoughts. A psychiatric consult is obtained. During his interview, he states that he cannot control his thoughts, and he appears agitated and restless. He has elated and grandiose thoughts but is not delusional. He reports no suicidal thoughts. He is found to be in the initial stages of an acute bipolar I episode.

29. Which type of acute episode is T.R. most likely experiencing?
A. Mania. B. Mixed episode.
C. Depression. D. Rapid cycling.

30. T.R.'s physician wants to initiate a second-generation antipsychotic (SGA). Which antipsychotic should be avoided in this patient?
    A. Aripiprazole. B. Brexpiprazole.
    C. Ziprasidone. D. Risperidone.
31. Which feature in T.R.'s history would best indicate that he has bipolar I disorder, not bipolar II disorder?
    A. His current mood is manic.
    B. He has a history of a major depressive episode.
    C. He is not delusional.
    D. He does not have suicidal thoughts.
32. G.B. is a 45-year-old woman who presents to the primary care clinic with nonspecific feelings of pain, fatigue, sadness, and irritability as well as difficulty sleeping. Her medical history includes allergies, for which she takes cetirizine 10 mg orally daily. Her score on a PHQ-9 is 15. On questioning, you learn that she recently decreased the time she spends gardening and reading, saying she cannot concentrate. She is going to work but has difficulty getting out of bed in the morning. She cannot identify any recent traumatic events in her life. Which is the best first-line drug therapy for G.B.?
    A. Sertraline. B. Selegiline patch.
    C. Aripiprazole. D. Amitriptyline.

Questions 33 and 34 pertain to the following case.

D.B. is a 22-year-old man who presents to the clinic 10 days after discharge from St Amanuel Hospital after a first-episode schizophrenia. He has no other chronic medical conditions and takes no routine medications except for risperidone. His dose was titrated over 2 weeks to 6 mg orally at bedtime for command hallucinations and persecutory delusions. He has a history of opioid use and does not use tobacco; he drinks alcohol only occasionally. He is a full-time college student studying accounting. His auditory hallucinations are well controlled, but he had feelings of inner restlessness that worsened when the risperidone dose was increased from 4 mg to 6 mg.

33. Which is the best initial treatment?
    A. Change to olanzapine 10 mg orally at bedtime.
    B. Consider risperidone 50 mg IM every 2 weeks.
    C. Decrease risperidone to 4 mg orally at bedtime.
    D. Change to clozapine 25 mg orally at bedtime.
34. When D.B. returns to the clinic 2 weeks later, he continues to endorse feelings of inner restlessness. He cannot sit through his 2-hour lectures, and his friends have commented on how "antsy" he appears all the time. He is concerned about adverse effects, but he has been adherent. He is wary of

changing medications because of complete resolution of his hallucinations. To address his concerns, which medication is most appropriate?

A. Diphenhydramine.
B. Propranolol.
C. Lorazepam.
D. Benztropine.

35. A 57 – year –old man with long term schizophrenia has been maintained on a new anti-psychotropic drug. Now he reports that there are frequent incidences of seizure since he started taking medication. All other findings are normal. What is the most likely drug that is responsible for his complaint?

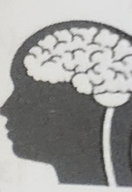
A. Clozapine
B. Olanzapine
C. Risperidone
D. Ziprasidone

36. A 28 – year –old man with manic – depressive disorder has maintained on Lithium carbonate for two years and his mood was stable in those years. Now, he reports a gradual onset of fatigue, weight gain and cold intolerance. What is the most likely laboratory test to diagnosis his problem?

A. Thyroid – stimulating hormone
B. Hepatic function panel
C. Glucose tolerance test
D. Hematocrit

37. A psychotic patient is taking Haloperidol 15 mg PO QD. To decrease mild effects of the drug Trihexyphenidyl 5 mg PO QD was added. What could be the possible side effect of the added drug?

A. Diarrhea
B. Dryness of mouth
C. Excessive sweeting
D. Nausea and Vomiting



CHAPTER 8: NEUROLOGIC DISORDERS

8.1. Seizure and Epilepsy

Definitions

- ***Seizure***: a paroxysmal event due to an abnormal, excessive discharges from excessive excitation and synchronization of a population of cortical neurons.
- ***Epilepsy***: a clinical condition of recurrent (two or more) seizures due to a chronic, underlying process

Epidemiology

- Epilepsy is the fourth most common neurologic disorder globally; only following stroke, migraine, and Alzheimer disease. About 50 million people worldwide have epilepsy. About 50% of patients with a new diagnosis become seizure free on their first treatment, with up to 70% becoming seizure free after treatment adjustment. In developing countries, the incidence is higher at 100 to 190 cases per 100,000 persons per year. New-onset seizures occur most frequently in infants younger than 1 year of age and in adults after age 55.

Social Impacts of Epilepsy

- Epileptic patients are restricted on driving
- About 50% patients with epilepsy report cognitive and learning difficulties.
- Transportation and educational difficulties combined with persistent seizures to cause unemployment (underemployment), and as a result, problems with paying for health care.
- The social stigma of embarrassment or injury due to seizures in public results in isolation of the patient

Risk Factors

- Premature birth with small gestational weight
- Perinatal injury (eg, anoxia)
- History of alcohol withdrawal seizures
- History of febrile seizures, and
- Family history of seizures

Etiology of Seizure and Epilepsy

- **Genetic Etiology**: usually present in infancy or childhood
  1) ***Dravet syndrome*** associated with mutations in sodium channel, voltage-gated, type 1 alpha subunit (SCN1A),
  2) ***Childhood absence epilepsy (CAE)*** associated with many different mutations in T-type Ca^{2+} channels and GABA-receptor subunits, and

3) ***Juvenile Myoclonic Epilepsy*** (JME) associated with many different mutations including those in the EF-hand containing protein-1 (EFHC1) and intestinal cell kinase (ICK).

- **Structural Etiology:** abnormalities visible on structural neuroimaging, and are either acquired or of genetic origin
- **Infectious Etiology:** Typically occurs when a patient develops epilepsy as the sequelae of an infection. The most common acquired infectious epilepsy is from neurocysticercosis, a parasitic infection of the brain that results from ingestion of pork tapeworm eggs.
- **Metabolic, Immune, and Unknown Etiology**
  - ✓ ***Metabolic***: Lafora disease, which is associated with abnormal glycogen metabolism and subsequent development of insoluble glycogen inclusion bodies resulting in epilepsy
  - ✓ ***Immune*** epilepsies include anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis which causes autoimmune-mediated central nervous system (CNS) inflammation and resulting epilepsy
- Seizure is the result of shift in the normal balance of excitation and inhibition within the CNS. Adolescence and young adult: head trauma, drug intoxication and withdrawal. Older adult: stroke, brain tumor, acute metabolic disturbances, eurodegenerative

✍ **Factors that precipitate seizures (triggers)**

- Hyperventilation
- Photostimulation (flashing lights or rapidly changing or alternating images)
- Physical and emotional stress,
- Sleep deprivation,
- Sensory stimuli,
- Hormonal changes occurring around the time of menses, puberty, or pregnancy
- Medications: theophylline, high-dose phenothiazines, antidepressants (bupropion), alcohol and substance use

✍ **Pathophysiology**

- The general pathophysiologic process for all epilepsies is neuronal ***hyperexcitability*** and ***hypersynchronization***
- Initially during a seizure, a small number of hyperexcitable neurons fire abnormally in synchrony resulting in breakdown of normal membrane conductances and inhibitory synaptic currents. This allows the excess excitability to spread, either locally to ***produce a focal seizure***, or the seizure is propagated by physiologic pathways and networks to involve more remote areas, or more widely to produce a ***generalized seizure***
- Neuronal hyperexcitability occurs because there is an enhanced predisposition of a neuron to depolarize and discharge when stimulated

- ✓ Alterations in the number, type, and biophysical properties of voltage- or ligand-gated K+, Na+, Ca2+, and Cl– ion channels in neuronal membranes
- ✓ Alterations in vesicle trafficking and neurotransmitter release
- ✓ Alterations in neurotransmitter uptake and metabolism
- ✓ Biochemical modifications of receptors,
- ✓ Modulation of second messaging systems and gene expression, and
- ✓ Changes in extracellular ion concentrations

✍ Clinical Presentation of Seizure

1) *Focal Aware Seizures*

- Patients retain awareness of themselves and their environment including external stimuli.

2) *Focal Impaired Awareness Seizure*

- Patient has impaired awareness at any time during the seizure. Patient may be able to respond to questions during the seizure, but inappropriate respons. He may not recall actions after event
- Motor signs include
  - ✓ Automatisms: automatic behaviors like lip smacking, chewing, picking at clothing
  - ✓ Atonic: loss of tone, going limp
  - ✓ Clonic: rhythmic jerking or twitching of arm, shoulder, face, or leg
  - ✓ Spasm: trunk flexion
  - ✓ Hyperkinetic: thrashing/pedaling
  - ✓ Myoclonic: arrhythmic jerking of arm, shoulder, face, or leg
  - ✓ Tonic: extension or flexion postures
- Non-motor signs include
  - ✓ Autonomic: flushing, sweating, piloerection, salivation, pallor
  - ✓ Behavior arrest: pausing, freezing, activity arrest
  - ✓ Cognitive: language problems, thinking problems, memory phenomenon, and feelings of familiarity (***déjà vu***) or unfamiliarity (***jamais vu***)
  - ✓ Emotion: feelings of fear, depression, joy, anger, extreme aberration of behavior
  - ✓ Sensory: numbness, tingling, sounds (ringing/buzzing), smells, tastes, visions (hallucinations), vertigo

3) *Focal to Bilateral Tonic–Clonic*

- Focal seizure with impaired awareness which progresses to bilateral convulsive features such as with tonic–clonic motor features

4) *Generalized Onset*

- There is impaired awareness
- ***Motor signs***

- ✓ **Tonic–clonic:** sudden sharp tonic stiffening of muscles with a subsequent period of clonic movements such as rhythmic jerking of arms and legs. There are five phases of a primary tonic-clonic seizure: flexion, extension, tremor, clonic, and postictal. During the ***flexion phase***, the patient's mouth may be held partly open, and the patient may experience upward eye movement, involvement of the extremities, and loss of consciousness. In the ***extension phase***, the patient may be noted to extend his or her back and neck; experience contraction of thoracic and abdominal muscles; be apneic; and have flexion, extension, and adduction of the extremities. The patient may cry out as air is forced from the lungs in this phase. The ***tremor phase*** occurs as the patient goes from tonic rigidity to tremors and then to a clonic state. During the ***clonic phase***, the patient will experience rhythmic jerks. The length of the entire seizure is usually 1–3 minutes. After the seizure, the patient may be ***postictal***. During this time, the patient can be difficult to arouse or somnolent. Before the seizure, a patient may experience a ***prodrome*** but not an aura. Sudden sharp tonic contraction of muscles followed by a period of rigidity and clonic movements.
- ✓ **Clonic**: rhythmic jerking or twitching of arm, shoulder, face, or leg
- ✓ **Myoclonic**: arrhythmic jerking of arm, shoulder, face, leg
- ✓ **Atonic**: loss of tone, going limp
- ✓ **Epileptic spasms**: trunk flexion

- ***Nonmotor (absence)***
  - ✓ Typical: sudden arrest of behavior, blank stare with brief upward
  - ✓ Eyelid myoclonia: lid jerks

✍ Epilepsy syndroms

- Common epilepsy syndromes include childhood
  - ✓ Childhood absence epilepsy (CAE)
  - ✓ Juvenile absence epilepsy (JAE)
  - ✓ Juvenile myoclonic epilepsy (JME)
  - ✓ West syndrome
  - ✓ Lennox–Gastaut syndrome (LGS)
  - ✓ Dravet syndrome

✍ Diagnosis

- Epilepsy is a clinical diagnosis, meaning that it is made on the basis of medical signs and patient-reported symptoms, rather than any one diagnostic test.
- A person is considered to have ***epilepsy*** if they meet any of the following conditions:

  1) ***at least two unprovoked*** (or reflex) seizures occurring greater than 24 hours apart;

2) ***one unprovoked*** (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or
3) diagnosis of an epilepsy syndrome

- **EEG**: it identifies abnormal brain wave patterns that are associated with certain seizure types and epilepsy syndromes. It is one of the most common and important diagnostic tests that can be performed for a patient with epilepsy. An abnormal epileptiform EEG is found in only approximately 50% of the patients who have epilepsy and sometimes several EEGs must be obtained
- **Brain imaging** with either CT or MRI can detect structural lesions that aid in the diagnosis of seizures and epilepsy types. A CT is commonly performed in patients who present after their first seizure, as a way to evaluate for a brain tumor, cerebral bleeding, or gross anatomical injury. ***An MRI is preferred*** for epilepsy diagnosis as it is the preferred imaging technique to identify more subtle structural abnormalities (eg, sclerosis in the mesial temporal lobes and traumatic brain injury).

✍ Management of Epilepsy

- **Desired Outcome**
  - ✓ Controlling seizures, however, in 20% to 35% of patients, complete seizure freedom may not be possible
  - ✓ Avoiding treatment side effects, and
  - ✓ Maintaining or restoring quality of life
- Antiseizure medications (ASM) therapy is the mainstay of epilepsy treatment; however, all available ASMs are symptomatic treatments which only prevent seizures from occurring. *None have been proven to have any disease modifying or antiepileptogenic properties and no ASMs are curative.*
- The optimal treatment plan for epilepsy includes
  - ✓ An accurate diagnosis of the patient's seizure type(s),
  - ✓ An objective measure of the intensity and frequency of the seizures,
  - ✓ Awareness of medication side effects, and
  - ✓ An evaluation of disease-related psychosocial problems.
- A working knowledge of available ASMs: mechanisms of action, PK, DDIs, and adverse effects, is essential
- Treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with AEDs or surgery, and addressing a variety of psychological and social issues.

✍ *Treatment of underlying conditions*

- ✓ Treatment of metabolic disturbance such as an abnormality of serum electrolytes or glucose

- ✓ Avoidance of drugs that caused the seizure (e.g., theophylline) or illicit drug use (e.g., cocaine)
- ✓ Appropriate treatment of underlying lesions (a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess)

✍ *Avoidance of precipitating factors*

- ✓ Patient who has seizures in the setting of sleep deprivation should obviously be advised to maintain a normal sleep schedule
- ✓ Modify alcohol drinking habits
- ✓ Stress reduction techniques such as physical exercise, meditation, or counseling

- **When to start antiseizure medication therapy**
  - ✓ ***First unprovoked seizure***: the decision of whether or not to start antiseizure medication therapy at the time of a first unprovoked seizure depends on
    1) The risk for recurrent seizures
    2) Benefit of early versus deferred treatment
    3) The side effect profiles of various ASM options,
    4) Patient values and preferences
  - ✓ Increased risk for ***seizure recurrence after a first unprovoked seizure***
    - ↳ Epileptiform abnormalities on EEG
    - ↳ Remote symptomatic causes (brain tumor, brain malformation, head injury with loss of consciousness, prior CNS infection, or scarring from a prior brain injury or brain surgery)
    - ↳ Abnormal neurologic examination, including focal findings and intellectual disability
    - ↳ A first seizure that occurs during sleep (ie, a nocturnal seizure)

> **Key Concepts** ***Unprovoked seizure*** *refers to a seizure of unknown etiology as well as one that occurs in relation to a preexisting brain lesion or progressive nervous system disorder (referred to as a remote symptomatic seizure).* ***Provoked seizures*** *are due to an acute condition such as a toxic or metabolic disturbance, immediately antecedent head trauma, or very recent/acute stroke (ie, acute symptomatic seizures).*

  - ✓ **Second unprovoked seizure**: patients presenting with a second unprovoked seizure should be started on antiseizure medication therapy since seizure recurrence indicates that the patient has a substantially increased risk for additional seizures
- Factors to consider when making ASM selection
  - ✓ ASM efficacy for the specific seizure type, epilepsy, or epilepsy syndrome

- ✓ Selection of an ASM that can also treat the patient's other comorbid conditions
- ✓ Selection of an ASM with the most tolerable adverse effect profile, considering patient-specific factors including age and sex
- ✓ Interactions with other medications
- ✓ Ability to adhere to a prescribed regimen (eg, 3 or 4 times daily dosing)
- ✓ Need to quickly reach therapeutic levels

- **Optimizing Doses of ASMs**
  - ✓ Once an ASM has been selected, it should be initiated at an appropriate starting dose, and gradually ***titrated up*** to a therapeutic maintenance dose based on individual ASM recommendations
  - ✓ Titration to an adequate therapeutic dose usually occurs ***over a few weeks*** and is necessary to allow the patient to slowly adjust to dose-related adverse effects
  - ✓ Some individuals, such as older adults who are sensitive to falls, sedation, and other neurocognitive adverse effects, need to ***have lower doses started and titrated more slowly***. In such cases, titration can last ***over many weeks or months*** and may have a lower goal dose.
  - ✓ In patients with ***multiple recent seizures***, a therapeutic dose needs to be reached much more quickly, and a ***rapid titration over days*** instead of weeks is appropriate. For such patients, loading doses, either administered orally or intravenously, may be indicated. It is important to select ASMs that can be administered safely as loading doses, as medications like lamotrigine and topiramate require slow titration and should not be used in patients who require loading to reach therapeutic levels quickly
  - ✓ Determining the optimal therapeutic dose for an individual takes into account ***treatment response*** and ***adverse medication reactions***.
  - ✓ If the patient is seizure free with no adverse reactions at a minimal therapeutic dose, an optimal dose has been achieved and no further increases is necessary.
  - ✓ If the patient continues to have seizures at a minimal or moderate-therapeutic dose, further titration to a maximum dose may be needed for optimal seizure control.
  - ✓ If the patient continues to have seizures at a maximum dose, or if the patient experiences intolerable adverse reactions at any dose adding a second ASM and then tapering and discontinuing the ineffective or intolerable first ASM is appropriate. Selecting an ASM with a different mechanism of action than the first intolerable or ineffective ASM may increase the likelihood of success with the second ASM,

> **Key Concepts** *In general,* ***ASM monotherapy*** *is preferred. However, if the patient continues to have seizures after switching to a second ASM as monotherapy at a therapeutic dose,* ***dual ASM therapy*** *may be necessary, and an adjunctive ASM should be gradually added*

- ✓ Selection of an adjunctive ASM with a different or complementary mechanism of action is recommended and is the basis behind rational polytherapy,
- ✓ For individuals who continue to have seizures on dual ASM therapy, polytherapy with three or more agents can be considered.

- **Anti-Seisure Medications (ASMs)**

I) First generation ASMs

- ✓ ***Carbamazepine (CBZ)***: Indicated fo monotherapy/adjunctive therapy for ***focal onset, TC***, and ***mixed seizure*** types except for absence seizures Mechanism of action is sodium channel blockade. Adverse effects include rash (occurs after a delay of 2–8 weeks), syndrome of inappropriate antidiuretic hormone release, aplastic anemia, thrombocytopenia, anemia, leukopenia. Extended-release tablets 100, 200, and 400 mg; extended-release capsules 100, 200, and 300 mg are available. Do not crush or chew these extended tablets. Extended-release capsules can be opened and sprinkled on food. ***Ghost tablets*** can be seen in the stool with the extended-release tablets. Patients with the *HLA-B*1502* allele are at a 10-fold elevated risk of SJS. Testing is recommended for Asians (including Indians). More than 15% of populations in Hong Kong, Malaysia, the Philippines, and Thailand have this allele.
- ✓ ***Clonazepam (CLZ):*** Binds to $GABA_A$ receptor and potentiates GABA by modulating chloride conductance. It is indicated as monotherapy/adjunctive therapy for Lennox-Gaustat Syndrome (petit mal variant), akinetic, myoclonic, and absence seizures. It may increase TC seizures when used in mixed seizure types; tolerance and dependence may occur; risk of respiratory depression which is increased when used with other CNS depressants including opioids; contraindicated in acute narrow angle glaucoma and severe hepatic impairment; withdrawal symptoms including status epilepticus may occur after discontinuation. ADRs include ***serious but rare***: blood dyscrasias including leukopenia, thrombocytopenia, eosinophilia; respiratory depression; hepatomegaly; muscle weakness; ***long term***: physiologic dependence; hair loss; hirsutism; ankle and facial edema
- ✓ ***Ethosuximide (ESM)***: Mechanism of action is by blocking T-type calcium channel. Useful only for absence seizures. May worsen generalized TC

seizures and other seizure types when used alone in mixed types of epilepsy; contraindicated in those with allergies to succinimides; may cause fetal harm; use with caution in hepatic/renal dysfunction. Common ADRs includes: GI distress including nausea/vomiting, cramps diarrhea; epigastric and abdominal pain; anorexia and weight loss; CNS effects including lethargy, fatigue, drowsiness, dizziness, ataxia. Long-term ADRs: behavioral changes

- ✓ ***Phenobarbital (PHB):*** Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance: used for focal onset and generalized seizures. Easily available world-wide; extensive knowledge and experience with PHB use. Tolerance and dependence may occur; slow taper needed when discontinuing after prolonged use; use with other CNS depressants may produce additive CNS effects; may cause respiratory depression; can cause fetal harm. ***Common ADRs*** include: CNS effects such as residual sedation or "hangover," impaired cognition, drowsiness, dizziness, vertigo, ataxia, headache, sleep disturbance; paroxysmal effects including excitement, irritability and hyperactivity in older adults and children; GI effects including epigastric pain, nausea, vomiting, diarrhea and constipation. ***Serious but rare ADRs:*** respiratory depression and apnea; rash (SJS, TEN); cardiac effects including bradycardia, hypotension with IV administration, syncope; hepatotoxicity; megaloblastic anemia; apnea and hypoventilation. ***Long term ADRs***: Behavioral changes; connective tissue disorder; intellectual blunting; metabolic bone disease (Rickets, osteopenia, osteoporosis, osteomalacia); folate deficiency (with megaloblastic anemia)
- ✓ ***Phenytoin (PHT):*** Enhances fast inactivation of voltage-gated sodium channels; inhibits persistent sodium current (INAP) and increases threshold for action potential firing. Indicated as: monotherapy or adjunctive therapy for focal onset psychomotor seizures and TC seizures; prevention or treatment of seizures during or after neurosurgery, severe traumatic brain injury, status epilepticus. May aggravate seizures in patients with absence seizures; can increase blood sugar levels in diabetes; HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry; CYP2C9*3 carriers may increase development of SCARS; monitoring of free phenytoin levels required in renal, hepatic impairment, hypoalbuminemia, and pregnancy. ***Common ADRs***: CNS effects including ataxia, nystagmus, slurred speech, decreased coordination, mental confusion, dizziness, insomnia, transient nervousness, headaches. ***Serious but rare ADRs***: blood dyscrasias including thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia; lymphadenopathy; rash (SJS/TEN/SCARS); DRESS; hepatotoxicity; angioedema: bradycardia/cardiac arrest; purple

glove syndrome with IV administration. ***Long term ADRs***: Connective tissue changes including skin thickening, gingival hyperplasia, coarsening of facial features, enlargement of lips; hirsutism; metabolic bone disease (osteoporosis, osteopenia, osteomalacia); peripheral neuropathy; cerebellar atrophy; folate deficiency (with megaloblastic anemia)

- ✓ ***Fosphenytoin (FOS)***: Mechanism of action it is prodrug for phenytoin; fast sodium channel blocker. Parenteral formulation for loading or maintenance dosing in place of phenytoin; status epilepticus. Phenytoin equivalents are used; 1 mg of phenytoin = 1.5 mg of fosphenytoin.
- ✓ ***Primidone (PRM):*** Prodrug converted to active metabolite phenylethylmalonamide-amide (PEMA) and phenobarbital with same mechanism of action, Indicaed for monotherapy/adjunctive therapy for focal onset and TC seizures. ***Common ADRs:*** CNS effects including ataxia, vertigo, nystagmus, diplopia, drowsiness, fatigue; GI effects including nausea/vomiting, anorexia, fatigue; emotional disturbances including hyperirritability. Serious but rare ADRs: Blood dyscrasias including granulocytopenia, agranulocytosis; rash (SJS, TEN); liver dysfunction. Long term ADRs: behavioral changes; intellectual blunting; connective tissue disorder; metabolic bone disease (rickets, osteomalacia); folate deficiency (with megaloblastic anemia)
- ✓ **Valproate (VPA):** potentiates GABAergic transmission among multiple other unknown mechanisms. Indicated as monotherapy or adjunctive therapy for focal onset and multiple seizure types for patients ≥10 years of age; monotherapy/adjunctive therapy for absence seizures in patients ≥10 years of age. Contraindicated in significant **hepatic dysfunction**; Use with caution in pancreatitis, bleeding and other hematopoietic disorders; Risk of hyperammonemia with and without encephalopathy associated with concomitant topiramate use; **Pregnancy category D** – contraindicated in women of childbearing potential and pregnancy category X for pregnant patients treated for migraine prophylaxis. ***Common ADRs***: GI effects including abdominal pain/GI upset (worse with valproic acid IR), constipation, diarrhea, anorexia, increased appetite, weight gain, nausea/vomiting; CNS effects including blurred vision, ataxia, dizziness, headache, insomnia, nystagmus, somnolence, thinking abnormal, tremor; dose dependent thrombocytopenia (>100 mg/mL). ***Long-term ADRs***: Hair and nail changes including alopecia, hirsutism, hair texture and color changes, nail and nail bed disorders; irregular menses and polycystic ovary-like syndrome; weight gain; cerebral pseudoatrophy; osteoporosis and osteopenia

2) Second-Generation ASMs

- ✓ **Felbamate (FBM)**: Mechanism of action it blocks glycine site on *NMDA* receptor. Serious adverse effects: Hepatotoxicity, aplastic anemia. Patient or guardian must sign consent form. Used only when seizures are severe and refractory to other medications, and when the benefit clearly outweighs the potential adverse effects

- ✓ **Gabapentin (GBT)**: Mechanism of action is through nhibition of α2δ subunit of voltage-dependent calcium channels. Extended-release tablets 300 and 600 mg are available. Indication: Adjunctive therapy for focal onset seizures with and without TC seizures in patients ≥3 years. Useful in post-herpetic neuralgia, chronic pain, and neuropathy; few interactions. ***Common ADRs***: CNS effects including somnolence, dizziness, ataxia, fatigue, nystagmus; peripheral edema and weight gain; GI effects including nausea/vomiting. ***Serious but rare ADRs***: Anaphylaxis, angioedema, DRESS, neuropsychiatric symptoms in children 3 to 12 years of age. ***Long-term ADRs***: Weight gain, peripheral edema.
- ✓ **Lamotrigine (LTG)**: mechanism of action by decreasing glutamate and aspartate release, delays repetitive firing of neurons, blocks fast sodium channels. Rash is a primary concern; lamotrigine must be titrated slowly to avoid a rash. Indication: Adjunctive therapy in focal onset and TC seizures, generalized seizures of LGS in patients ≥2 years of age; monotherapy in patients with focal-onset seizures ≥16 years of age. Valproic acid decreases lamotrigine metabolism; this interaction requires even slower titration with lower initial and final doses. Estrogen-containing oral contraceptives increase lamotrigine clearance; therefore, twice the amount of lamotrigine may be necessary. ***Common ADRs***: CNS effects including dizziness, headache, diplopia, ataxia, blurred vision, somnolence, tremor; GI effects including nausea/vomiting, abdominal pain, diarrhea; other effects including rhinitis, pharyngitis, infection, fever; rash. ***Serious but rare ADRs***: DRESS; blood dyscrasias; Rash usually appears after 3-4 weeks of therapy and is typically generalized, erythematous, and morbilliform but can progress to SJS
- ✓ **Levetiracetam (LEV)**: Mechanism of action can prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. Extended-release tablets (500 mg, 750 mg) are available for once-daily dosing. ***Common ADRs***: CNS effects including somnolence, fatigue; behavior effects including aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability. ***Serious but rare ADRs***: Psychosis, hallucinations
- ✓ **Oxcarbazepine (OXC)**: Mechanism of action it is fast sodium channel blocker Adverse effects: Hyponatremia more common than with carbamazepine (increased dose and increased age increase risk of hyponatremia); blood dyscrasias less common than with carbamazepine; 25%–30% of patients with hypersensitivity to carbamazepine will have hypersensitivity to oxcarbazepine; rash. Extended-release tablets are

available (150, 300, 600 mg). ***Common ADRs:*** CNS effects including dizziness, somnolence, diplopia, fatigue, ataxia, abnormal vision, headache, nystagmus, tremor; GI effects including nausea, vomiting; hyponatremia due to SIADH; rash. ***Serious but rare ADRs***: SJS, TEN; DRESS; blood dyscrasias

- ✓ **Topiramate (TPM):** Antagonizes voltage-gated sodium channel; binds to GABAA receptor and augments GABAergic transmission, antagonizes AMPA/kainate glutamate receptor, weak carbonic anhydrase inhibitor. Indicated as monotherapy/adjunctive therapy for focal onset seizures or primary generalized TC seizures in patients ≥2 years of age; adjunctive therapy for patients with LGS ≥2 years of age. Useful in comorbid migraine and obesity; XR useful in non-adherence as dosed once dail. Avoid in patients with preexisting cognitive issues; renally dose adjust with CrCl <70 mL/min; can cause fetal harm. ***Common ADRs***: CNS effects including fatigue, difficulty concentrating, confusion, language problems, tremor paresthesias; behavioral effects including nervousness, anxiety. ***Serious but rare ADRs***: Renal stones, glaucoma, hypo/erthermia, oligohidrosis, metabolic acidosis, SJS, TEN, and hyperammonemia with and without encephalopathy when used with valproate. ***Long term ADRs***: Weight loss; renal stones; metabolic acidosis.

✍ **Non-pharmacologic treatment**

- Approximately 20% to 35% of patients will not achieve adequate seizure control and seizures may be considered medication-resistant
- Nonpharmacologic therapy for epilepsy includes: diet, vagus nerve stimulation (VNS) and surgery
- **The ketogenic diet:** Devised in the 1920s, is high in fat and low in carbohydrates and protein, which leads to a shift in metabolism resulting in acidosis and ketosis. As protein and calorie intake are set at levels that will meet requirements for growth, most of the calories provided come in the form of heavy cream and butter, although medium-chain triglycerides can be substituted for the dietary fats. Furthermore, no sugar is allowed, the overall fluids are controlled, and vitamins and minerals are supplemented

Table 8.1. Medication Selection for Various Seizure Types

Drug	Focal	Generalized Motor	Absence	Atonic	Myoclonic	Infantile spasm	Dravet syndrome	LGS
Brivaracetam	3	—	—	—	—	—	—	—
Carbamazepine	1	1	—	4	4	—	—	—
Cenobamate	4	—	—	—	—	—	—	—
Clobazam	4	4	3	—	3	—	2	1
Clonazepam	—	—	—	1	2	2	—	1
Diazepam	—	—	—		4	4	—	2
Eslicarbazepine	4	—	—	—	—	—	—	—
Ethosuximide	—	—	1	—	4	—	—	—
Felbamate	5	5	5	—	5	—	—	5
Gabapentin	1	2	—	—	—	—	—	—
Lacosamide	1	—	—	—	—	—	—	—
Lamotrigine	1	1	2	3	3	—	—	1
Levetiracetam	1	1	4	—	3	—	1	—
Lorazepam	3	3	3	—	3	—	—	—
Oxcarbazepine	1	1	—	3	3	—	—	—
Phenobarbital	2	2	2	—	3	—	—	—
Phenytoin	2	2	—	—	3	—	—	—
Pregabalin	4	—	—	—	—	—	—	—
Primidone	2	2	2	—	—	—	—	—
Topir amate	1	1	3	3	1	—	—	—
Valproic acid	2	1	1	1	1	1	2	—
Vigabatrin	5	5	—	—	—	5	—	—
Zonisamide	1	3	3	—	4	—	—	—

1 = first-line drug; 2 = second-line drug; 3 = some therapeutic effect; 4 = adjunctive therapy; 5 = used only when benefits outweigh risks; LGS = Lennox Gastaut Syndrome

Table 8.2 Starting and maximal adult seizure medicine doses[1]

Drug	Starting dose	Usual maximum dose
Carbamazepine	200 mg twice daily	1600 mg/day
Clonazepam	0.5 mg 3 times/day	20 mg/day
Ethosuximide	250 mg twice daily	1.5 g/day
Felbamate	400 mg 3 times/day	3600 mg/day
Gabapentin	300 mg 3 times/day	3600 mg/da
Lamotrigine	With valproic acid: **25 mg qod**	With valproic acid: **200 mg/day**
	Without carbamazepine, phenytoin, phenobarbital, or valproic acid: **25 mg/day**	Without carbamazepine, phenytoin, phenobarbital, or valproic acid: **375 mg/day**
	With carbamazepine, phenytoin, phenobarbital, and not with valproic acid: **50 mg/day**	With carbamazepine, phenytoin, phenobarbital, and not with valproic acid: **500 mg/day**
Levetiracetam	500 mg twice daily	3000 mg/day
Oxcarbazepine	300 mg twice daily	2400 mg/day
Phenobarbital	1–3 mg/kg/day	300 mg/day
Phenytoin	100 mg 3 times/day	600 mg/day
Pregabalin	75 mg twice daily	600 mg/day
Topiramate	25–50 mg/day	1000 mg/day
Valproic acid	10–15 mg/kg/day	60 mg/kg/day

- **Vagus nerve stimulation (VNS):** The VNS consists of an implanted pulse generator implanted below the clavicle and lead that is wrapped around the left vagus nerve in the carotid sheath. FDA approved implanted medical device that is used as adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years of age with focal seizures refractory to ASMs. It is also used off-label in the treatment of refractory primary generalized epilepsy. The mechanisms behind VNS's antiseizure actions are unknown. VNS changes the CSF concentration of inhibitory and stimulatory neurotransmitters and increased blood flow.

Monitoring of Therapy

- Most anticonvulsant drugs need to be introduced relatively slowly to minimize side effects. Patients should expect that minor side effects such as mild sedation, slight changes in cognition, or imbalance will typically resolve within a few days
- Monitoring of serum antiepileptic drug levels is required. If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it is necessary to add another AED. This is

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[1] Bondi DS, Bridgeman MM, Burke JM, et al. **Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course,** 2021 ed. Lenexa, KS: American College of Clinical Pharmacy, 2021

usually done by maintaining the patient on the first drug while a second drug is added.

✍ When to Discontinue Therapy[1]

- It is reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the following criteria:
  - ✓Complete medical control of seizures for 1 to 5 years;
  - ✓Single seizure type, either partial or generalized;
  - ✓Normal neurologic examination, including intelligence;
  - ✓Normal EEG.
- In most cases it is preferable to reduce the dose of the drug gradually over 2 to 3 months. Most recurrences occur in the first 3 months after d/c therapy.

✍ Epilepsy and Pregnancy

Key Concepts *Epilepsy-related complications during pregnancy include possible changes in seizure frequency, fluctuating ASM plasma levels, and possible teratogenic effects of ASMs.*

- ***Fluctuations in ASM concentration*** may be caused by physiologic changes that occur during pregnancy including reduced gastric motility, nausea and vomiting, increased medication distribution, increased renal elimination, altered hepatic enzyme activity as well as changes in protein binding. Patients on ***lamotrigine*** have been found to undergo a 40% decrease in the ratio of plasma lamotrigine concentration to dose, resulting in deterioration of seizure control in approximately 75% of pregnant patients. It is therefore recommended that ASM levels, particularly lamotrigine levels, be monitored closely during pregnancy, and that dosage increases occur over the course of the pregnancy if needed.
- Adverse pregnancy outcomes associated with ASM use include an increased risk of ***major congenital malformations*** **(MCMs)** compared to pregnant persons without epilepsy.

Key Concepts *The most concerning effects are found with the use of* ***valproic acid*** *which is associated with a risk of MCMs that is 3.5 to 4 times that of offspring from patients without epilepsy, especially if taken during the first trimester of pregnancy.*

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[1] American Academy of Neurology: **Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients--summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology.** *Neurology* 1996, 47(2):600-602.

- ❖ IV Phenytoin or fosphenytoin PE adults: 10 to 20 mg/kg at rate of 50 mg/min or 150 mg/min PE, respectively; infants/children: 15 to 20 mg/kg at a rate of 1 to 3 mg/kg/min

3) Established status (30 – 60 min)
   - ↳ Seizure continues:
   - ❖ Additional IV 5 mg/kg dose of either phenytoin or fosphenytoin PE may be given in unresponsive patients
   - ❖ IV Phenobarbital 20 mg/kg at a rate of 100 mg/min in adults and 30 mg/min in infants/children
4) Refractory status (> 60 min)
   - ↳ Clinical or electrical seizures continue:
   - ❖ IV Phenobarbitala additional 10 mg/kg; 10 mg/kg may be given every hour until seizures stop or
   - ❖ IV Valproate 15–25 mg/kg followed by 1 to 4 mg/kg/hourb or
   - ❖ General anesthesia with IV midazolam, or IV pentobarbital or IV propofol

Key Concepts ***Lorazepam** is less lipid soluble than diazepam and takes longer to achieve peak concentrations in the brain; however, its minimal redistribution into fat results in a longer CNS duration of action, providing seizure protection for up to 24 hours. It also has a higher-affinity binding to the benzodiazepine receptor compared to diazepam.*

8.2. Parkinson's Disease

Definition

- Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities. The disorder was first described by **James Parkinson** in his 1817 Essay on the Shaking Palsy. PD result from a reduction of dopaminergic transmission within the basal ganglia.

Epidemiology

- With epidemiological studies in 1980s, the prevalence of PD in Sub-Sahara Africa ranged from 7/100,000 in Ethiopia to 67/100,000 in Nigeria.[1]
- Its peak age of onset is in the 60s (range is 35 to 85 years). Familial clusters of autosomal dominant and recessive forms of PD comprise 5% of cases

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[1] Williams U, Bandmann O, Walker R: **Parkinson's Disease in Sub-Saharan Africa: A Review of Epidemiology, Genetics and Access to Care.** *J Mov Disord* 2018, 11(2):53-64.